



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 600

[Docket No. FDA-2017-N-7007]

RIN 0910-AH49

Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule amending the general biologics regulations relating to time of inspection requirements and also removing duties of inspector requirements. FDA is taking this action to remove outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug and device establishments, thereby providing flexibility without diminishing public health protections. This action is part of FDA's implementation of Executive Orders (E.O.s) 13771 and 13777. Under these E.O.s, FDA is comprehensively reviewing existing regulations to identify opportunities for repeal, replacement, or modification that will result in meaningful burden reduction, while allowing the Agency to achieve our public health mission and fulfill statutory obligations.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the "Search" box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Jenifer Stach, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

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### I. Executive Summary

#### *A. Purpose of the Final Rule*

FDA is issuing this final rule to amend the general biologics regulations relating to time of inspection requirements and to remove duties of inspector requirements. FDA is taking this action to remove outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug and device establishments, thereby providing flexibility without diminishing public health protections.

#### *B. Summary of the Major Provisions of the Final Rule*

This final rule revises the time of inspection requirements contained in § 600.21 (21 CFR 600.21) and also removes the duties of inspector requirements contained in § 600.22 (21 CFR 600.22). These changes to the biological product regulations eliminate outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug and device establishments, thereby providing flexibility without diminishing public health protections. Revision and removal of these regulations does not change the biological product establishment inspection requirements and duties of an investigator requirements that apply under sections 704 and 510(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374 and 360(h)) and section 351(c) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(c)).

### *C. Legal Authority*

FDA is taking this action under the biological product provisions of the PHS Act, and the drugs and general administrative provisions of the FD&C Act, including sections 704 and 510(h) of the FD&C Act and section 351(c) of the PHS Act.

### *D. Costs and Benefits*

Because this final rule does not impose any additional regulatory burdens, this regulation is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

## **II. Background**

### *A. Need for this Rulemaking*

In the *Federal Register* on January 26, 2018, FDA published a proposed rule entitled "Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products; Companion to Direct Final Rule" (83 FR 3631), as well as a companion direct final rule entitled "Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products" (83 FR 3586). To allow for consideration of the issues raised in the comments to the proposed rule, FDA withdrew the direct final rule in the *Federal Register* of May 7, 2018 (83 FR 19936). After careful consideration of these issues, FDA is issuing this final rule to revise the time of inspection requirements contained in § 600.21 and to remove the duties of inspector requirements contained in § 600.22. As discussed in the proposed rule, on February 24, 2017, President Donald Trump issued E.O. 13777, "Enforcing the Regulatory Reform Agenda" (82 FR 12285, March 1, 2017). One of the provisions in the E.O. requires Agencies to evaluate existing regulations and make recommendations to the Agency head regarding their repeal, replacement, or modification, consistent with applicable law. As one step

in implementing the E.O., FDA published a notice in the *Federal Register* of September 8, 2017 (82 FR 42492) entitled "Review of Existing Center for Biologics Evaluation and Research Regulatory and Information Collection Requirements." In that notice, FDA announced that it was conducting a review of existing regulations to determine, in part, whether they can be made more effective in light of current public health needs and to take advantage of, and support, advances in innovation that have occurred since those regulations took effect. As part of this initiative, FDA is updating outdated regulations as specified in this rule.

FDA's general biological products regulations in part 600 (21 CFR part 600) are intended to help ensure the safety, purity, and potency of biological products administered to humans. The revision and removal of certain general biological products regulations are designed to eliminate outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for drug and device establishments, and provide flexibility without diminishing public health protections. Specifically, this final rule revises § 600.21 and removes § 600.22.

#### *B. Summary of Comments to the Proposed Rule*

We received five comments on the proposed rule from individual submitters. We received comments both in support of the proposed rule and comments raising concerns over the proposed revisions to §§ 600.21 and 600.22. These comments are further summarized in section IV.

#### *C. General Overview of the Final Rule*

As discussed in the proposed rule (83 FR 3631 at 3633), FDA's authority to conduct establishment inspections is included in both the FD&C Act and the PHS Act. Specifically, section 704 of the FD&C Act and section 351(c) of the PHS Act authorize the Agency to inspect

establishments that manufacture biological products. Following enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) on July 9, 2012, and as provided under the provisions in E.O. 13777, FDA is revising § 600.21 and removing § 600.22.

FDA is revising § 600.21 to remove the biennial inspection requirement for biological product establishments that are registered as drug establishments and for those that are registered as device establishments. Before FDASIA was signed into law, section 510(h) of the FD&C Act provided, among other things, that drug and device establishments registered with FDA must be inspected on a biennial basis. Section 510(h) of the FD&C Act applies to biological product establishments because all biological products are subject to regulation under the drug or device provisions of the FD&C Act (in addition to the biological product provisions of the PHS Act). Since 1983, FDA's biological product regulation at § 600.21 has also included a biennial inspection requirement, which was consistent with the pre-FDASIA biennial inspection requirement in section 510(h) of the FD&C Act.

With the enactment of FDASIA, however, the biennial inspection requirement for drug establishments in section 510(h) of the FD&C Act was replaced with a requirement that FDA inspect drug establishments in accordance with a risk-based schedule established by FDA. Additionally, the FDA Reauthorization Act of 2017 (FDARA) was signed into law on August 18, 2017, and substantively amended the FD&C Act to, among other things, revise section 510(h)(2) such that the biennial inspection schedule for device establishments was also replaced by a risk-based schedule. FDA has determined that the biennial inspection requirement in § 600.21 regarding the frequency of inspections is outdated and no longer consistent with the FD&C Act (e.g., the risk-based inspection schedule for drug and device establishments may

result in scheduling inspections at intervals of greater or less than 2 years for certain biological product establishments).

FDA is also removing provisions in § 600.21 concerning inspectional notice and the timing of pre-licensure reinspections of biological product establishments, as these provisions are outdated and unnecessary. As discussed in the proposed rule (83 FR 3631 at 3634), inspectional notice is addressed in the Agency's practices for inspections in its Standard Operating Procedures and Policies and in the Investigations Operations Manual (IOM). With respect to the timing of a reinspection of a biological product establishment following the denial of a biologics license application, the general biologics licensing provision at 21 CFR 601.4, which was issued subsequent to § 600.21, sets forth the administrative procedures following the denial of a license; accordingly, the specific provision in § 600.21 regarding timing of a reinspection following denial of a license is unnecessary.

FDA has further decided that current § 600.22, which requires specific duties of an FDA inspector, is unnecessary because the requirements in § 600.22(a) through (h) are duplicative of statutory requirements that apply to biological product inspections under section 704 of the FD&C Act. Specifically, the inspection requirements in section 704 of the FD&C Act encompass all of the requirements outlined in § 600.22. Thus, we are removing § 600.22(a) through (h).

The removal of these regulations, however, does not change the establishment inspection requirements and duties of investigator requirements specified in sections 704 and 510(h) of the FD&C Act, section 351(c) of the PHS Act, or the procedures described in the IOM. Additionally, it does not change the established process for risk-based inspection planning and work planning.

### III. Legal Authority

FDA is issuing this rule under the biological products provisions of the PHS Act (42 U.S.C. 216, 262, 263, 263a, and 264) and the drugs and general administrative provisions of the FD&C Act (21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, and 379k-l). Under these provisions of the PHS Act and the FD&C Act, we have the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, and potent, and to prevent the introduction, transmission, and spread of communicable disease.

### IV. Comments on the Proposed Rule and FDA Response

#### *A. Introduction*

We received five comments on the proposed rule from individual submitters. We describe and respond to the comments in sections IV. B through IV. C. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number and, in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance, or the order in which comments were received.

#### *B. Description of Comments Regarding Revisions to §§ 600.21 and 600.22*

(Comment 1) One comment supported the proposed rule.

(Response 1) We acknowledge and appreciate the supportive comment.

(Comment 2) One comment expressed concern that the risk-based inspection frequency will not be without negative health consequences. The comment also stated that "[R]isk Management is an identified known weak element to a majority of biological and medical device



companies" and that the management and mitigation of risk without FDA oversight for a number of years is going to be a high-risk endeavor.

(Response 2) We disagree that the risk-based inspection frequency will have negative health consequences. The purpose of this rule is to remove outdated requirements and accommodate new approaches, such as a risk-based inspection frequency for device and drug establishments. We believe this final rule will provide flexibility without diminishing public health protections. Furthermore, as discussed in the preamble to the proposed rule (83 FR 3633), establishing a risk-based schedule for inspections of drug establishments registered with FDA was mandated with the enactment of the FDASIA that was signed into law on July 9, 2012. In August 2017, FDARA mandated a risk-based schedule for inspections of device establishments registered with FDA. As a result of these amendments to the FD&C Act, sections 510(h)(2) and (3) of the FD&C Act now include requirements to establish a risk-based schedule for the inspection of drug and device establishments. In accordance with section 510(h)(4) of the FD&C Act, the risk-based schedule must consider, among other things, the known safety risks of such establishments, including the compliance history of the establishment; the record, history, and nature of recalls linked to the establishment; the inherent risk of the drug or device manufactured, prepared, propagated, compounded, or processed at the establishment; the inspection frequency and history of the establishment; and any other criteria deemed necessary and appropriate by FDA. While we agree that application of the risk-based inspection frequency may result in some establishments being inspected less frequently than every 2 years, these establishments will have been determined to be at a lower risk based on the Agency's evaluation of the above factors. In addition, the resources saved by performing less frequent inspections at lower risk establishments will allow FDA to inspect those establishments deemed higher risk

more frequently if needed. Therefore, we believe the comment's concerns about negative health consequences are addressed during FDA's review of the known safety risks of drug and device establishments. The known safety risks that FDA must consider in establishing a risk-based schedule are outlined in section 510(h)(4) of the FD&C Act. With regard to "[R]isk Management," we note that any such discussion is outside the scope of this rule.

(Comment 3) One comment expressed concern with FDA's implementation and process for the review of existing regulations under E.O. 13771.

(Response 3) We reiterate that the purpose of this rule is to remove outdated requirements and accommodate new approaches, such as the risk-based inspection frequency for drug and device establishments required by the FD&C Act, and to provide flexibility without diminishing public health protections. With regard to FDA's implementation and process for the review of existing regulations under E.O. 13771, we note that any such discussion is outside the scope of this rule.

(Comment 4) One comment expressed concern with respect to determining the frequency of inspections and asserted that any revised risk-based inspection schedule should provide for "both more relaxed and more frequent forms of inspection, if indicated by the conditions and risks that are assessed." The comment also asserted that FDA must "recognize that for products or processes for which quality is important and significant failures of quality are unacceptable, there may be a need for inspection more frequently than every two years, and with the degree of inspection and discussion now contained in the inspector duties under 600.20."

(Response 4) As discussed in the preamble to the proposed rule (83 FR 3633), the risk-based inspection schedule for drug and device establishments *may* result in scheduling inspections at intervals of greater than 2 years for *certain* biological product establishments.

However, those establishments will have been determined to be at a lower risk based on evaluation of the factors included in section 510(h)(4) of the FD&C Act. In addition, the resources saved by performing less frequent inspections at lower risk establishments will allow FDA to inspect those establishments deemed higher risk more frequently when needed. We reiterate that the removal of these regulations will not change the establishment inspection requirements and duties of an investigator requirements specified in sections 704 and 510(h) of the FD&C Act and section 351(c) of the PHS Act. Additionally, it will not change the established process for risk-based inspection planning and work planning. Furthermore, this revision will not change FDA's authority to inspect an establishment for special cause, such as when FDA becomes aware of consumer complaints or adverse event reports, signaling a possible product quality issue for which a prompt inspection may be useful in investigating the matter. Therefore, while we agree, in part, with the comment, we believe the concerns expressed in the comment are addressed through FDA's review of the known safety risks of drug and device establishments and by FDA's ability to inspect as needed in the interest of patient safety. The known safety risks that FDA must consider in establishing a risk-based schedule are outlined in section 510(h)(4) of the FD&C Act.

#### *C. Description of Comments Outside the Scope of This Rulemaking*

(Comment 5) One comment requested an exemption to newly created Occupational Safety and Health Administration (OSHA) requirements.

(Response 5) We decline to respond because the request is outside the scope of this rule.

#### **V. Economic Analysis of Impacts**

We have examined the impacts of the final rule under E.O. 12866, E.O. 13563, E.O. 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform

Act of 1995 (Pub. L. 104-4). E.O. 12866 and E.O. 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). E.O. 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that this final rule is not a significant regulatory action as defined by E.O. 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule does not impose any additional regulatory burdens, we certify that this final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

This rule is being issued to amend the general biologics regulations by removing certain time of inspection requirements and the duties of inspector requirements. This action is being taken to remove outdated requirements, accommodate new approaches, and provide flexibility

without diminishing public health protections. Because this rulemaking would remove regulations to be consistent with updated practice and does not impose any additional regulatory burdens, this rulemaking is not anticipated to result in any compliance costs and the economic impact is expected to be minimal.

#### VI. Analysis of Environmental Impact

We have determined under 21 CFR 25.31(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### VIII. Federalism

We have analyzed this final rule in accordance with the principles set forth in E.O. 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

#### IX. Consultation and Coordination with Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in E.O. 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or

on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

#### List of Subjects in 21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 600 is amended as follows:

#### PART 600--BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for part 600 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, 379k-l; 42 U.S.C. 216, 262, 263, 263a, 264.

#### § 600.21 [Amended]

2. Amend § 600.21 by removing the last three sentences.

#### § 600.22 [Removed and Reserved]

3. Remove and reserve § 600.22.

Dated: March 25, 2019.

Scott Gottlieb,

Commissioner of Food and Drugs.

[FR Doc. 2019-06187 Filed: 4/1/2019 8:45 am; Publication Date: 4/2/2019]